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08/782,590

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/782,590	01/13/97	ROSE	

EXAMINER	
S 4	

ART UNIT	PAPER NUMBER
UNGAR, S 1642	18

HM21/1125

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DATE MAILED: 11/25/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/2/98

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-87 is/are pending in the application.
Of the above, claim(s) 1-68 + 84-87 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 69-83 is/are rejected.
☑ Claim(s) 69 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☑ Interview Summary, PTO-413 3 Sheets
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1. The Amendment filed September 21, 1998 (Paper No. 14) in response to the Office Action of February 25, 1998 (Paper No. 10)is acknowledged and has been entered. Previously pending claims 63-84 have been amended. Claims 63-83 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

3. The following objections are being maintained:

Objection to the specification in Paper No. 10, Section 3, page 4 for the reasons previously disclosed.

Applicant argues that pages 14-16 contain a description of each of the drawing of Figures 1-44. The argument has been noted but has not been found persuasive because a review of the specification revealed that there is not an adequate description of each drawing. For example, the drawings are replete with numbers (for example, see Figure 36) which are not defined or described in any way in the Brief Description of the Drawings.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claims 69-83 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 5(a) pages 5-8.

Applicant argues (a) that the making of soluble precipitable material is disclosed in the specification at pages 20-23 and the making of soluble precipitable material comprising of soluble and insoluble moieties is disclosed in the specification at pages 23 and 24, (b) the effective dosage and the methods of administration can be the same as the prior art described as "ADEPT" on pages 9

and 10, © the soluble precipitable material is deliberately made so that it is insoluble and will precipitate by the action of an enzyme as set forth on pages 20-24, (d) the effective dosage and the methods of administration can be the same as the prior art described as "ADEPT" on pages 9 and 10, (e) the bispecific reagent is biologically inactive, (f) the word "adapted has been replaced in claims 69, 74, 75, 76 and 84 and effective dosage and methods of administration can be the same as the prior art describe as "ADEPT", (g) the action is referring to the soluble precipitable material as being a protein or peptides and proteins are not being claimed and the specification does not describe proteins and peptides as candidates for the soluble precipitable material, (h) the making of soluble precipitable material is disclosed in the specification at pages 20-3 and the making of soluble precipitable material comprised of soluble and insoluble moieties is disclosed in the specification at pages 23-24, (I) the insoluble precipitate produced by the present invention does not diffuse away and does not move away by convection into the lymphatics because tumor tissue lacks an effective lymphatic drainage and if necessary the precipitate is tethered to various structure. The arguments have been noted but are not been found persuasive because (a') a review of the cited support reveals general teachings of the chemistry of indoxyl chemistry but does not provide either guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo.* Further, the issue raised here is not only whether the making/using of soluble precipitable material is disclosed in the specification but also that applicant has not taught how to make or use the instant invention, especially in view of Applicant's (page 15, section 21 of Paper No. 14) admission on the record that the therapeutic agent is "only therapeutic after it has

been converted into an insoluble material because the therapeutic effect depends on the radiation field which is generated by the precipitate induced immobilization of the isotope and its long term retention at the immobilized site". A review of the specification does not reveal the absolutely critical nature of radio-labeling of the therapeutic agent, (b') a review of pages 9 and 10 reveals the disclosure of numerous references which report the enzymatic conversion of a pro-drug to an active drug in the extracellular space, however, none of the cited references have been submitted and therefore none of the references have been considered. However, it is noted that on page 10, paragraph 2, the specification clearly states that "ADEPT approach fails to successfully treat cancer", thus dosage and methods of administration used in the prior art would not be expected to enable the instant claims, further, it is noted that the cited references are to be found in the "Prior Art" section of the specification and that neither guidance on nor exemplification of administration or exemplification of or guidance for effective dosage are to be found in the portion of the specification drawn to the invention (c' and d'). As disclosed above the teachings on page 20-24 are drawn to indoxyl chemistry and no teaching or exemplification is provided for any of the other therapeutic reagents claimed and the argument is not found persuasive for the reasons disclosed in section (b') above, (e') the argument is drawn to the bispecific reagent, however, as clearly repeated on page 8 of the response, the issue raised here is that the therapeutic agents may be inactivated *in vivo* and because applicant did not distinctly and specifically point out the supposed errors rejection, the rejection is maintained, (f') although the word "adapted" has indeed been replaced in the recited claims, the argument drawn to dosage and methods of administration is not found persuasive for the reasons set

forth in section (b') above, (g') as recited in claim 69, the term therapeutic agent includes peptides, carbohydrates, chitosan, chitin, proteoglycans and synthetic polymers as well as indoxyl compounds and contrary to applicant's arguments, peptides, which read on proteins, and proteoglycans are claimed. Claim 69 specifically claims that the therapeutic agent (as defined by the claim) is converted into a extracellular precipitate which the claim defines as an insoluble non-digestible precipitate and further Applicant admits on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material, (h') the argument is not persuasive for the reasons previously disclosed in section (a') and (c') above, (I') Applicant's stated opinion is noted but it is clear that one of skill in the art would expect that an insoluble precipitate would be removed from the claimed region either by convection, diffusion or by phagocytosis. Applicant is invited to submit objective evidence demonstrating that the insoluble precipitate will not diffuse away, move away or be removed from the area by phagocytosis. As drawn to the tethering of the precipitate, applicant is arguing limitations not recited in the claims as presently constituted. It is noted that amendment of the claims to recite tethering limitations in an amendment submitted after final would raise a new issue, not previously considered, and that the amendment would not be entered for this reason.

6. Claims 69-83 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 5(b) pages 8-10.

Applicant argues that loss of antibacterial activity is certain to develop, however with respect to the present invention this loss is irrelevant and actually required to convert a soluble indoxyl lactam into an insoluble indigestible material.

The arguments have been noted and has been found persuasive.

Applicant argues that (a) the present invention circumvents problems related to impermeability of tumors to antibodies and lack of uniform distribution of antibodies, (b) dosage methods of administration and the inactivation of the bispecific reagents are the same as in ADEPT which has circumvented the problems, © making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22 and 29-30 of the specification. The arguments have been noted but have not been found persuasive (a') because the issue raised here is not whether the instant invention circumvents problems related to impermeability of tumors to antibodies and lack of uniform distribution of antibodies, but rather whether the instant specification is enabling. For the reasons previously stated, one of skill in he art would be forced into undue experimentation to practice the claimed invention,(b') for the reasons previously disclosed in section 5(b') above, (c') a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p. 19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecule on pages 22 and 29-30.

7. Claims 69-83 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 5© pages 10-11.

Applicant argues that making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22 and 29-30 of the specification. The argument has been noted but has not been found persuasive for the reasons disclosed in 6(c') above.

8. Claims 69-83 remain rejected under 35 USC 112, first paragraph for the

reasons previously set forth in Paper No. 10, Section 5(d) page 11.

Applicant argues that making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22 and 29-30. The recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted but has not been found persuasive for the reasons disclosed in 6(c') above. Further, the issue raised here was not the definition of a large molecule that is cell impermeant but rather the issue raised was how to use a large molecule, as broadly claimed, that will function as claimed.

9. Claims 69-82 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 10, Section 6 pages 11-16.

Applicant argues that, as drawn to rejection 6(e) that the therapeutic agent is radio-labeled. The argument has been noted but has not been found persuasive as drawn to claims 69-82 because radio labeling is only claimed in claim 83 which is dependent upon claim 69.

Applicant argues that, as drawn to rejection 6(f) that as drawn to "disposed" the precipitate is formed by the catalytic action of the non-mammalian enzyme. The argument has been noted but has not been found persuasive because the term "disposed" has not been defined by either the claim or the specification.

Applicant argues that, as drawn to rejection 6(I) that the markush grouping is proper because the members of the group possess a property in common. The argument has been noted but is not persuasive because it is not clear whether the peptides and carbohydrates claimed are limited to those recited in the claim or whether they include other moieties of the same class.

Applicant argues that, as drawn to rejection 6(l), that making the soluble precipitable material into a cell impermeable is disclosed in the specification on pages 19, 22 and 29-30 and the recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted but has not been found persuasive a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p. 19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecule on pages 22 and 29-30 and does not define the claimed materials and further the recitation of weight of greater than 1000 Daltons does not define the metes and bounds of the claimed invention.

Applicant argues that, as drawn to rejection 6(s), see amendment to claim 79. The argument has been noted but has not been found persuasive because although the claim has been amended to recite the effects of altering indoxyl compounds, the claim has not been amended to define derivatives of benzyloxy compounds.

Claim Rejections - 35 USC § 102

10. Claims 69-82 remain rejected under 35 USC 102(b) for the reasons previously set forth in Paper No. 10, Section 8 pages 16-18.

Applicant argues that present invention comprises the conversion of a soluble precipitable material into an insoluble and non-digestible precipitate by the enzyme moiety of the bispecific reagent which remains adjacent to the bispecific reagent for an extended period of time thus the precipitate does not enter the system body fluids and that conversion of a soluble precipitable material into an insoluble and non-digestible precipitate is not shown or suggested by WO 91/109134 which recites only soluble, digestible active drugs that do not have epitopes and do not have neo-

epitopes which are not radioactive and are not used to bind any other bispecific reagents. The argument has been noted but has not been found persuasive because of the broadly recited prodrugs disclosed in WO 91/109134. Applicant is invited to submit objective evidence to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, particularly as drawn to the anti-cancer drugs recited on page 9, line 14 through page 11.

New Grounds of Objection

9. It is noted that, during the Interview of November 12, 1998 (Paper No. 16), Applicant informed Examiner that newly amended claim 69 (in Paper No. 14) had been submitted with several typographical errors in particular, on the third line from the bottom, after the words "the first bispecific reagent, into a", the term "soluble" is recited, however the intended term was "insoluble" and the typing of the term "soluble" was an inadvertent typographical error. Because of the extensive nature of the claim and the multiple amendments to the claim, the entire claim, as written was substituted for claim 69, entered from Paper No. 5. It is clear that, since no additions were indicated by underlining and no deletions were indicated by placing the word "insoluble" in brackets that the change was an inadvertent typographical error. Applicant is required to submit a corrected version of claim 69 with the typographical errors corrected to be substituted for the claim submitted in Paper No. 14).

New Grounds of Rejection

Claim Rejections - 35 USC § 112

11. Claims 69-83 are rejected under 35 USC 112, first paragraph, as the

specification does not contain a written description of the claimed invention. The limitation of "at least several days" in claim 69 and the limitation of "alter solubility, digestibility, color and physical state" in claims 78-80 have no clear support in the specification and the claims as originally filed. In a telephone interview with John Q. McQuillan on November 10, Examiner asked Mr. McQuillan to point to support for the amendment of the claims, to recite the newly cited limitations, in the specification and claims as originally filed. In a telephone interview with John Q. McQuillan on November 13, 1998, Mr. McQuillan did not point to support in the specification or claims as originally filed for the recited amendments. **The subject matter claimed in claims 69-83 broadens the scope of the invention as originally disclosed in the specification.**

12. All other objections and rejections recited in Paper No. 110 are withdrawn.

13. No claims allowed.

14. Applicant's amendment necessitated the new grounds of rejection.

Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT

TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER

Susan Ungar

November 14, 1998